in this population compared to what the normal distribution would be leads us to propose the following potential mechanisms for development of CHD in this population: local environmental factors or epigenetic factors influencing gene expression differentially in the twin pairs; reciprocal laterality signaling between twinned embryos during early development; or placental vascular factors that may contribute to severe valvar lesions leading to hypoplasia of the right or left heart or milder forms of valve disease in the setting of TTTS.

4–6

Fetal cerebral blood flow in congenital diaphragmatic hernia

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OBJECTIVES: Left ventricular cardiac output is decreased in fetuses with congenital diaphragmatic hernia (CDH). Our aim was to assess whether this alters cerebral perfusion or growth in utero. METHODS: Fetal head circumference, biparietal diameter, lung-to-head ratio and middle cerebral artery (MCA) Doppler flow patterns were assessed with ultrasound in 103 fetuses with prenatally diagnosed CDH. Total fetal lung volume and cerebral volume were measured using magnetic resonance imaging. Values were transformed to gestational age independent scores (multiples of the median; MoM) and compared with controls. Subanalyses were made according to whether the CDH was left (n=86) or right sided (n=17) and to whether it was isolated (n= 86) or associated with other anomalies (n=17). RESULTS: Middle cerebral artery flow velocity was significantly lower in CDH than in healthy fetuses (0.79 ± 0.19 MoM; $p < 0.0001$) but MCA pulsatility index was unchanged (0.99 ± 0.25 MoM; $p = 0.79$). Cranial biometry and cerebral volume in CDH fetuses fall in the normal range. Gestational age adjusted lung area was correlated with MCA peak systolic velocity which was in turn correlated with brain volume. CONCLUSION: Fetal cerebral perfusion is decreased in CDH yet cranial and cerebral growth are conserved. Further work will need to address whether part of the neurologic impairment observed in long-term survivors of CDH finds its origin in the prenatal period.

5–1

Novel insights into the pathogenesis of common aneuploidies using genomic analysis of amniotic fluid mRNA

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OBJECTIVES: As a novel means of identifying pathophysiologic changes in fetuses with common aneuploidies, we characterized developmental gene expression using cell-free mRNA in residual second trimester amniotic fluid (AF) supernatant samples. METHODS: RNA was extracted from AF in fetuses with trisomy 21 [T21] (n=7), trisomy 18 [T18] (n=5), and euploid controls (n=13). cDNA synthesis and biotin labeling were performed prior to hybridization to Affymetrix U133 plus 2.0 arrays. Initial analysis was done using the Affymetrix Gene Chip Microarray Suite 5.0, followed by comparative t-tests and Benjamini-Hochberg adjustment. Differentially-expressed genes were further examined using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) and Ingenuity®Pathways Analysis. RESULTS: In T21 we identified 414 differentially-expressed genes vs. euploid controls. Only 5/414 genes identified mapped to chromosome 21. In T18, only 7/356 differentially-expressed genes were on chromosome 18. Heat map and functional analyses of genes not on 18 or 21 showed consistent patterns that were unique for each aneuploidy but differed significantly from euploidy. Only 6 differentially-expressed transcripts were common to both aneuploidies. T21 samples showed significant oxidative stress and disruption in ion transport, G-protein signaling, immune response, and circulatory system function. T18 showed significant disruption of both the endocrine system and lipid metabolism. CONCLUSIONS: Residual AF samples provide a reproducible source of mRNA for genomic analysis of aneuploid fetuses. Our results question the conventional wisdom that the pathophysiology of aneuploidy is due to a gene dosage effect, as the molecular abnormalities observed here are predominantly produced by genes on chromosomes other than 18 or 21. Pathway analysis may provide new insights into each condition. For example, the down-regulation of the endocrine system may explain why fetuses with T18 are growth-restricted. This discovery-driven genomic approach using discarded material suggests new avenues to further understand fetal abnormal development and may suggest a personalized medicine approach to fetal therapy.